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(54) Title: ORAL OIL SORBING COMPOSITION

(57) Abstract

An oil sorbing delivery system is described. The system comprises an oil sorbing agent and is adapted to deliver the agent to the small or large intestine of a mammal. The oil sorbing agent can be calcium silicate or microcrystalline chitosan.

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ORAL OIL SORBING COMPOSITION

The present invention relates generally to a composition for use in the management of obesity. More particularly, the present invention relates to a composition which is adapted to absorb unwanted dietary fat in the small and/or large intestine of a patient, especially dietary fat which is either non-metabolizable or which has not been metabolized owing to treatment of the patient with drugs that inhibit the enzymatic conversion of the fats.

Obesity is a major problem in many Western countries with an estimate of over 30% of adults defined as clinically obese. Weight reduction can be achieved by the use of diet or pharmacological agents. Unfortunately, both approaches can lead to unpleasant side effects such as fat "leakage" or "spotting".

One approach to weight reduction via dietary measures involves the use of non-metabolizable fat substitutes such as Olestra. Olestra is known commercially as Olean™ and is available from Procter and Gamble (New Eng. J. Med. 334, 984 (1996)). The material is a polyester of sucrose and six or nine triglycerides and can be used to replace both vegetable and animal fats. Olestra adds the necessary texture and taste characteristics of fat, but is not metabolized in the intestine by the dietary lipases and, as a consequence, is not absorbed. However, if large quantities of food containing Olestra are consumed, then the excess fat can leak from the anal sphincter causing embarrassment and soiling of clothes. (Anon. Univ. California at Berkeley Wellness Lett. 12, 1-2 (986)).

In the body, fats (triglycerides) are converted enzymatically to fatty acids and diglycerides and these materials are then solubilised by bile salt

micelles and subsequently absorbed. One pharmacological treatment of obesity may involve the use of drugs that inhibit the enzymatic conversion of the fats to fatty acids and diglycerides, and a number of drugs are in development that act in this way. The mechanism can be one of preferential binding with lipases to prevent their interaction with dietary lipids. The compound Orlistat, Merck Index, 12, Edition P.6998 is a good example of a pancreatic lipase inhibitor (Obes. Res. 3 Suppl. 4, 6235, 1995). However, as with Olestra, the impaired metabolism of the dietary fat, e.g. by the administration of a lipase inhibitor, can result in anal leakage of fat material.

The use of chitosan as a food additive or as a pharmaceutical preparation to reduce the absorption of lipids is described in US-4,233,023. There is no suggestion in US-4,233,023 that chitosan could be delivered to the terminal ileum or the colon in a coated single unit dosage form. The examples given in US-4,233,023 describe food products and a powder that is dispersed in water or a flavoured vehicle before administration.

Thus, it would be advantageous to have a product that can reduce or even eliminate the leakage of non-metabolizable dietary fats or dietary fats which have not been metabolized owing to the use of drugs that inhibit their breakdown from the anal sphincter.

We have now found that it is possible to achieve this objective using a pharmaceutical composition that delivers an oil sorbing agent to the small and/or large intestine of man, especially the terminal ileum and/or proximal and transverse colon.

According to a first aspect of the present invention there is provided a composition comprising an oil sorbing agent characterised in that the composition is adapted to deliver the oil sorbing agent to the small or large intestine of a mammal, especially man.

According to a second aspect of the present invention there is provided an oil sorbing delivery system comprising an oil sorbing agent characterised in that the system is adapted to deliver the oil sorbing agent to the small or large intestine of a mammal, especially man.

By an "oil sorbing agent", we mean a material that when in contact with oil, either as oil alone or as oil dispersed in an aqueous medium at a pH between 5 and 8 or thereabouts, will sorb between 0.5 and 25 ml of oil per g thereof. Preferably, the oil sorbing agent will be capable of sorbing between 1 and 20 ml of oil, more preferably between 2 and 10 ml of oil per g thereof.

The term "oil" includes fats and dietary fats, fatty acids, tryglycerides, non metabolizable oils and fats.

The oil sorbing agent that is released into the small and/or large intestine, especially the terminal ileum and/or the proximal and transverse colon, to interact with dietary fat can be various in nature. By dietary fat, we mean any oleaginous material that is not absorbed in the small intestine and is a component of a food stuff. The term includes Olestra as well as vegetable and animal fats.

Suitable oil sorbing agents include calcium silicate, microcrystalline cellulose (Avicel™), dried aluminium hydroxide gels, microcrystalline

chitosan (as described by Struszczyk, J. Appl. Polymer Sci. 33, 177 1987 and available from Novasso OY, Finland), charcoal and porous carbon adsorbants such as the product AST-120 (available from Kurela Chemical Industry Co. Ltd., Japan and described in J. Pharm. Pharmac. 49 657, (1997)).

A suitable quantity of oil sorbing agent for administration to the patient is in the range of from 1 to 10 g per day. More preferably, from 1 to 5 g per day is administered on a fasted stomach.

Calcium silicate is a particularly preferred oil sorbing agent. A porous calcium silicate that sorbs oil is known as Florite and is available from Eisai Co. Ltd., Japan. This material is stated to sorb 5 ml of oil per g of sorbant. Calcium silicate is a material that is used in both pharmaceuticals and foods.

An especially preferred oil sorbing agent is microcrystalline chitosan.

The composition/delivery system of the invention may be a suitably coated single unit dosage form.

In one embodiment, the single unit dosage form is a tablet having a core comprising the oil sorbing agent and an outer coating or layer which surrounds the core and comprises a material which prevents release or any substantial release of the oil sorbing agent until the tablet reaches the small or large intestine. Preferably, the coating is adapted to prevent release of the oil sorbing agent in both the stomach and the upper regions of the small intestine, by which we mean the duodenum and jejunum, so that

release of the oil sorbing agent does not take place until the tablet reaches the terminal ileum or the large intestine, e.g. colon.

Tablets can be produced by direct compression of the oil sorbing agent (which is normally in powder, form) or by processes involving granulation in which the powder is wetted with a granulating agent, e.g. water, alcohol or a sugar solution, and the wet mass passed through a sieve to produce wet granules that are then dried, e.g. in a hot-air oven, prior to compression to form a tablet. Dispersion or disintegration aids, e.g. sodium starch glycolate (Explotab™), starches, lactose, croscarmellose sodium (Ac-Di-Sol™), can be added to the oil sorbing agent (see Pharmaceutical Dosage Forms : Tablets Volumes 1 and 2, H A Lieberman, L. Lackman and J. B. Schwartz (Eds), Marcel Dekker, Inc. New York 1989). The objective is to produce a single unit system comprising the oil sorbing agent that has sufficient mechanical strength to allow coating and subsequent handling, but which will disperse readily in the small or large intestine, especially the terminal ileum or colon, to provide a good surface area for fat sorption.

In another embodiment, the single unit dosage form is a capsule having a casing which encloses a compartment containing the oil sorbing agent and a barrier coating or layer on the outer surface of the casing which comprises a material which prevents release or any substantial release of the oil sorbing agent until the capsule reaches the small or large intestine. Preferably, the coating is adapted to prevent release of the oil sorbing agent in both the stomach and the upper regions of the small intestine, by which we mean the duodenum and jejunum, so that release of the oil sorbing agent does not take place until the tablet reaches the terminal ileum or the large intestine, e.g. colon.

When the oil sorbing agent is filled into a capsule, any of the capsules which have been fabricated to deliver medicaments to the human body may be employed. Suitable capsules include those made of hard gelatin, starch or hydroxypropylmethyl cellulose.

Starch capsules, e.g. as described in the United States Pharmacopoeia (USP), are preferred since these offer advantages in coating, i.e. in the storage and stability of the coating layer. Starch capsules having an outer coating of a material which is resistant to the conditions prevailing in the stomach and the upper regions of the small intestine such that release of the oil sorbing agent contained in the capsule is prevented or substantially prevented until the capsule reaches the terminal ileum and/or colon are preferably used in the present invention. Such capsules are described in PCT/GB95/01458.

By starch capsules we include capsules made from starch as well as capsules made from modified starches or starch derivatives. By the term "derivatives" we particularly mean esters and ethers of the parent compound that can be unfunctionalised or functionalised to contain, for example, ionic groupings.

Suitable starch derivatives include hydroxyethyl starch, hydroxypropyl starch, carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch, succinate derivatives of starch and grafted starches. Such starch derivatives are well known and described in the art (for example Modified Starches: Properties and Uses, O. B. Wurzburg, CRC Press Boca Raton (1986)).

The starches used should be of food or pharmaceutical quality.

The starch capsules can be made by an injection moulding process and typically comprise a body and a cap. The body is filled with the oil sorbing agent and the cap is then attached and sealed. Methods for making starch capsules are well known and are described, for example, in EP-A-118240, WO-90/05161, EP-A-0304401, WO-92/04408 and GB-2187703.

Methods for targeting the ileocaecal region and the colon can be found in PCT/US91/02319, EP-A-0454383, EP-A-0366621, US-4,432,966, GB-A-2292079, PCT/JP89/00748, PCT/US91/03014, PCT/SE91/00475, EP-A-0673645, US-4,663,308, WO-90/13286, GB-A-2174599, PCT/GB89/00581, GB-A-2166051, EP-A-0621032 and the papers by Watts and Illum, Drug Dev. Ind. Pharm. 23 (9) 893-914, 1997, and Wilding et al., Pharmac. Ther. 62, 97, (1994).

The oil sorbing agent may thus be filled into the various known delivery systems intended for targeting the ileocaecal and colonic regions, including those described in the above references.

Alternatively, the oil sorbing delivery system may take the form of a capsule containing granules or pellets of the oil sorbing agent which have been provided with an outer coating comprising a material which prevents release or any substantial release of the oil sorbing agent until the granules/pellets reach the small or large intestine.

The coating/layer in the above described delivery systems may be formed from an enteric material such as an enteric polymer that slowly dissolves

within the small intestine to allow exposure of the oil sorbing agent to the liquid in the terminal ileum and/or colon. Alternatively, the coating/layer may be formed from a polymeric material that is not degraded until it meets the specific conditions found in the colon. Such degradation may be through direct chemical decomposition, e.g. the degradation of disulphide bonds under reducing conditions, or the result of the microflora found within the colon which can bring about the degradation of polysaccharide materials.

Preferred enteric coating materials for targeting the ileocaecal or colonic regions which may be used to coat capsules, tablets or pellets are those which dissolve at a pH of 4.5 or above, e.g. a pH of 5.0 or above. In this way, the coatings only begin to dissolve once they have left the stomach and have entered the small intestine. A thick layer of coating is thus preferably provided which will dissolve in about 2 to 5 hours, thereby allowing the capsule shell or tablet core underneath to break-up only when it has reached the terminal ileum and/or the colon. Such coatings can be made from a variety of polymers such as cellulose acetate trimellitate (CAT), hydroxypropylmethyl cellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP) and shellac, as described by Healy in his article "Enteric Coatings and Delayed Release", Chapter 7 in *Drug Delivery to the Gastrointestinal Tract*, eds. Hardy et al, Ellis Horwood, Chichester, 1989. For coatings of the polymers, a thickness of 150 to 300 μm is suitable.

Especially preferred enteric materials are polymers comprising methyl methacrylate residues, such as methyl methacrylate homopolymers and copolymers of methyl methacrylate and methacrylic acid. Copolymers of

methyl methacrylate and methacrylic acid are available as Eudragit™ enteric polymers (Rohm Pharma, Darmstadt, Germany).

Preferred compositions are based on Eudragit L100 and Eudragit S100 as described in PCT/GB95/01458. Eudragit L100 dissolves at pH 6 and upwards while Eudragit S100 dissolves at pH 7 and upwards. Preferred coating compositions are based on Eudragit L100 and Eudragit S100 in the range 100 parts L100:0 parts S100 to 20 parts L100:80 parts S100. The most preferable range is 70 parts L100:30 parts S100 to 80 parts L100:20 parts S100. As the pH at which the coating begins to dissolve increases, the thickness necessary to achieve colon specific delivery decreases. For formulations where the ratio of Eudragit L100:S100 is high, a coat thickness of the order 150-200 μm is preferable. This is equivalent to 70-110 mg of coating for a size 0 capsule. For coatings where the ratio of Eudragit L100:S100 is low, a coat thickness of the order 80 to 120 μm is preferable, which is equivalent to 30 to 60 mg coating for a size 0 capsule.

The colonic region has a large population of microbial anaerobic organisms providing reducing conditions. Thus, the coating may suitably comprise a material which is redox sensitive. Such coatings may comprise azopolymers which may, for example, consist of a random copolymer of styrene and hydroxyethyl methacrylate, cross-linked with divinylazobenzene synthesised by free radical polymerisation (the azopolymer being broken down enzymatically and specifically in the colon), or disulphide polymers (see PCT/BE91/00006 and Van den Mooter, Int. J. Pharm, 87, 37 (1992)).

Another material which may be used to provide release in the colon is amylose or a complex thereof. For example, a coating composition can be

prepared by mixing an amylose-butan-1-ol complex (glassy amylose) with an ethyl cellulose aqueous dispersion (Ethocel™) (Milojevic et al., J. Control. Rel., 38, 75 (1996)). The final coating may comprise an inner layer of glassy amylose and an outer layer of cellulose or acrylic polymer material (Allwood et al., GB9025373.3). Other suitable coating materials include calcium pectinate (Rubenstein et al., Pharm. Res., 10, 258, (1993)); pectin - a polysaccharide which is totally degraded by colonic bacterial enzymes (Ashford et al., Br. Pharm. Conference, 1992 Abstract 13); chondroitin sulphate (Rubenstein et al., Pharm. Res. 9, 276, 1992); dextran hydrogels (Hovgaard and Brøndsted, 3rd Eur. Symp. Control. Drug Del., Abstract Book, 1994, 87); modified guar gum, such as borax modified guar gum (Rubenstein and Gliko-Kabir, S.T.P Pharma Sciences 5, 41 (1995)); p-cyclodextrin (Sie ke et al., Eur. J. Pharm. Biopharm, 40 (suppl), 335 (1994)); saccharide containing polymers, including methacrylic polymers covalently coupled to oligosaccharides such as cellobiose, lactulose, raffinose and stachyose and saccharide-containing natural polymers including modified mucopolysaccharides such as cross-linked chondroitin sulfate and metal pectin salts, for example calcium pectate (Sintov and Rubenstein; PCT/US91/03014); methacrylate galactomannan (Lehmann and Dreher, Proc. Int. Int. Symp. Control. Rel. Bioact. Mater. 18, 331 (1991)); pH-sensitive hydrogels (Kopecek et al., J. Control. Rel. 19, 121 (1992)) and resistant starches that are not broken down by the enzymes in the upper gastrointestinal tract but are degraded by enzymes in the colon, e.g. glassy amylose (Allwood et al., WO-89/11269, 1989).

The compositions/systems of the invention may also be adapted to deliver therapeutic agents, such as drugs that inhibit the enzymatic conversion of fats to fatty acids and diglycerides, to the small or large intestine of the

gastrointestinal tract, e.g. to the terminal ileum or the colonic region, especially the proximal colon. Preferably, a means is provided to prevent release of the drug until the formulation reaches the colonic region,

While the present invention is directed to treating the side effects of obesity treatments, it will be clear to the person skilled in the art that the invention could also be used to treat diseases that cause steatorrhea.

The present invention is now illustrated but not limited with reference to the following examples.

Example 1 Measurement of the in vitro fat binding properties of the oil sorbing agent calcium silicate

A method based on that of Nauss et al. Cancer Res. 43, 4083, (1983) was used. The oil sorbing agent was mixed with simulated intestinal contents. The oil binding capacity of the different materials was evaluated using standard procedures, for example 0.5g Florite was mixed with 4 ml of sesame oil. The oil was well incorporated into the powder. There was no evidence of free oil. A dispersion of 5 ml of vegetable oil (sesame oil) was dispersed into 50 ml of buffer at pH 7.00. The oil sorbing agent in different quantities was then dispersed into the buffer system and the quantity of fat removed measured by a binding isotherm determination where the fat remaining in the dispersed phase was determined using a standard analysis technique such as the Saxon method. (See for example Richterich and Colombo, Clinical Chemistry, Wiley, 1981)

The binding studies were conducted on the oil sorbing agent dosed into the buffer system as a powder as well as in the form of an uncoated single unit

system such as a tablet or capsule that subsequently disperse into the buffer system.

The oil was well incorporated into the oil sorbing agent. There was no evidence of free oil.

Example 2 Measurement of the in vitro fat binding properties of the oil sorbing agent microcrystalline chitosan

Into each of two 50 ml measuring cylinders was poured 25 ml of water and 25 ml of sunflower oil (Sainsbury's, London, UK). To one of the cylinders was added 1 gram of microcrystalline chitosan (Novasso Oy, Finland, molecular weight 150 kDa, degree of deacetylation 74%). Both cylinders were stoppered, inverted 10 times and left to stand overnight. In the sample containing no microcrystalline chitosan, the oil formed a clear layer on top of the water (Figure 1.). In the sample containing microcrystalline chitosan, the majority (in excess of 20 ml) of the oil had formed into globules around 1 to 5 mm in diameter (Figure 1). The formation of these stable globules appeared to be a result of accumulation of microcrystalline chitosan particles at the oil-water interface.

Example 3 Measurement of the in vitro fat binding properties of the oil sorbing agent microcrystalline chitosan (high viscosity environment)

To simulate a system with a viscosity more comparable to the contents of the colon, an aqueous solution containing 1.6% hydroxypropyl methylcellulose (HPMC) was prepared: 400 ml of water was heated to 80°C and 16 grams of Methocel E10M grade HPMC was added

(Colorcon, Orpington, UK). The HPMC was dispersed into the hot water and the dispersion transferred to an ice bath. Stirring was continued until a viscous gel had formed. The mixture was removed from the ice bath and adjusted to 1000 ml with water. 200 ml of HPMC solution and 20 ml of sunflower oil was added to each of two glass beakers. 0.8 grams of microcrystalline chitosan (see Example 2) was added to one of the beakers. The contents of each beaker were stirred thoroughly and then left to stand overnight. In the sample containing no microcrystalline chitosan, the oil formed a clear layer on top of the HPMC solution. In the sample containing microcrystalline chitosan, there was no free oil visible at the surface of the beaker. The upper half of the beaker content had a yellow colouration, suggesting that the oil resided in dispersed form in this portion of the sample.

Example 4 Adsorption of fat by microcrystalline chitosan in the presence of faecal material

Faeces were obtained from three female cross-bred pigs and pooled. The following formulations were evaluated in duplicate.

(1) 25g of the faeces, 10 ml soya oil (CWS, Manchester, UK) and 100 ml water.

(2) As for (1) plus 1g of microcrystalline chitosan (Novasso Oy, Finland).

(3) As for (2) but 2g of the microcrystalline chitosan was used.

The mixtures were agitated vigorously and allowed to settle over a period of 24 hours. A simple oil/water mixture was used as a control.

For samples not containing chitosan, 2 to 8 mls of oil could be recovered by simple separation. For the samples containing 1g and 2g of microcrystalline chitosan, there was no free oil present that could be separated.

Example 5 In vivo evaluation of fat sorption

The effect of the oil sorbing agent on the faecal excretion of fat in rats fed on high fat diet can be measured using the method described by Deuchi et al. Biosci. Biotech. Biochem. 59 781 (1995). In this method the oil sorbing agent is included in the experimental diet that contains corn oil and lard (40%). The animals are fed the diet for 13 days. Faecal lipids are measured gravimetrically by a standard method (e.g. Saxon) (see Richterich and Colombo, Clinical Chemists, Wiley 1981). An apparent fat digestability value is obtained.

The ability of a single unit dosage form and the oil sorbing agent contained therein to effect fat adsorption in vivo is determined using a fistulated pig. The pig has a fistula in the intestines in the region of the terminal ileum. This allows direct access to the large intestine and is, therefore, a suitable model for the evaluation of a system that targets a material to the colon or ileocaecal junction of man. The model used is described by Garner et al. J. Pharm. Pharmac. 48, 689, (1996). Uncoated single units are placed into the colon through the ileal fistula where they are able to break up to release their contents. Pigs are provided with a diet to provide steatorrhoea. The faeces are collected for

36 hours after dosing using a metabolic cage system. The faecal fat content of treated and untreated animals is measured using a standard assay for fat content (see for example Richterich and Colombo, Clinical Chemistry, Wiley, 1981).

Example 6 Tablet formulation

A tablet system was prepared by the direct compression of 500 mg microcrystalline chitosan containing 25 mg of croscarmellose sodium as a dispersing agent. The tablets were made using a Manesty F3 machine with 20 mm x 8 mm oblong concave punches. The tablets were coated with a layer of enteric polymer (3:1 ratio of Eudragit L:S with plasticiser and talc in isopropanol) to provide a thickness equivalent to a 90 mg increase in average tablet weight. The tablets were coated by a standard method of spray coating using an Aeromatic STREA-1 coater (standard column) drying temperature 25°C, fan speed 6, atomization pressure 1 bar. A pan coater could also be used. The ability of the tablets to remain intact at an acid pH (stomach conditions) and release their contents after 2 hours in alkaline conditions (to simulate transit in the small intestine and release of the adsorbent in the distal colonic region) was determined using a standard USP Dissolution apparatus (Type 1) employing buffers at pH 2 and pH 6.8. The tablets were exposed to acid conditions for 2 hours and remained in tact. After exposure to the alkaline conditions, the coating dissolved and the tablets released their contents.

Example 7 Capsule formulation

Starch capsules (USP) were obtained from Capsugel, Switzerland. The capsules were filled with 500 mg of calcium silicate (Florite). The

capsules were then coated as in Example 3 to provide a weight gain of 90 mg.

Claims:

1. A composition comprising an oil sorbing agent characterised in that the composition is adapted to deliver the oil sorbing agent to the small or large intestine of a mammal.

2. A composition according to claim 1 which is adapted to provide release of the oil sorbing agent in the colonic region of the large intestine.

3. A composition according to claim 1 which is adapted to provide release of the oil sorbing agent in the terminal ileum of the small intestine.

4. An oil sorbing delivery system comprising an oil sorbing agent characterised in that the system is adapted to deliver the oil sorbing agent to the small or large intestine of a mammal.

5. A system according to Claim 4 in the form of a tablet having a core comprising the oil sorbing agent and an outer coating or layer which surrounds the core and comprises a material which prevents release of the oil sorbing agent until the tablet reaches the small or large intestine.

6. A system according to Claim 4 in the form of a capsule having a casing which encloses a compartment containing the oil sorbing agent and a barrier coating or layer on the outer surface of the casing which comprises a material which prevents release of the oil sorbing agent until the capsule reaches the small or large intestine.

7. A system according to Claim 6, wherein the capsule comprises a casing of gelatin, starch or hydroxypropylcellulose.

8. A system according to claim 7, wherein the capsule is a starch capsule.

9. A system according to any one of claims 5 to 8, wherein the coating is adapted to prevent release of the oil sorbing agent until the system reaches the terminal ileum or the colonic region.

10. A system according to any one of claims 5 to 9, wherein the coating comprises an enteric material.

11. A system according to claim 10, wherein the enteric material will only dissolve at a pH of 4.5 and above.

12. A system according to claim 10 or claim 11, wherein the enteric material is a polymer.

13. A system according to Claim 12, wherein the polymer is a methacrylate polymer comprising methyl methacrylate residues.

14. A system according to Claim 13, wherein the methacrylate polymer is a copolymer of methyl methacrylate and methacrylic acid.

15. A system according to any one of claims 5 to 9, wherein the coating comprises a material which degrades under reducing conditions.

16. A system according to Claim 15, wherein the material is a polymer containing azo or disulphide groupings that are preferentially degraded in a colonic environment.

17. A system according to any one of claims 4 to 16, wherein the oil sorbing agent is selected from the group consisting of microcrystalline chitosan, dried aluminium hydroxide gel, microcrystalline cellulose and calcium silicate.

18. A system according to Claim 17, wherein the oil sorbing agent is calcium silicate.

19. A system according to Claim 17, wherein the oil sorbing agent is microcrystalline chitosan.

20. A system according to any one of Claims 4 to 16, wherein the oil sorbing agent can sorb between 1 and 20 ml per g.

21. A composition according to any one of Claims 1 to 3 which further comprises a drug which inhibits the enzymatic conversion of fats or otherwise blocks the uptake of fat from the gastrointestinal tract.

22. A system according to any one of Claims 4 to 20 which further comprises a drug which inhibits the enzymatic conversion of fats or otherwise blocks the uptake of fat from the gastrointestinal tract.

23. A method for adsorbing undigested and non-digestable fat from the small or large intestine of a mammal which comprises administering a composition according to any one of Claims 1 to 3 to the mammal.

24. A method for adsorbing undigested and non-digestable fat from the small or large intestine of a mammal which comprises administering a system according to any one of Claims 4 to 20 to the mammal.

25. A method according to Claim 23 or Claim 24 in which a drug which inhibits the enzymatic conversion of fats or otherwise blocks the uptake of fat from the gastrointestinal tract is administered concurrently with the system or composition.

26. The use of an oil sorbing agent in the manufacture of a composition which is adapted to deliver the oil sorbing agent to the small or large intestine of a mammal.

27. The use of an oil sorbing agent in the manufacture of an oil sorbing delivery system which is adapted to deliver the oil sorbing agent to the small or large intestine of a mammal.

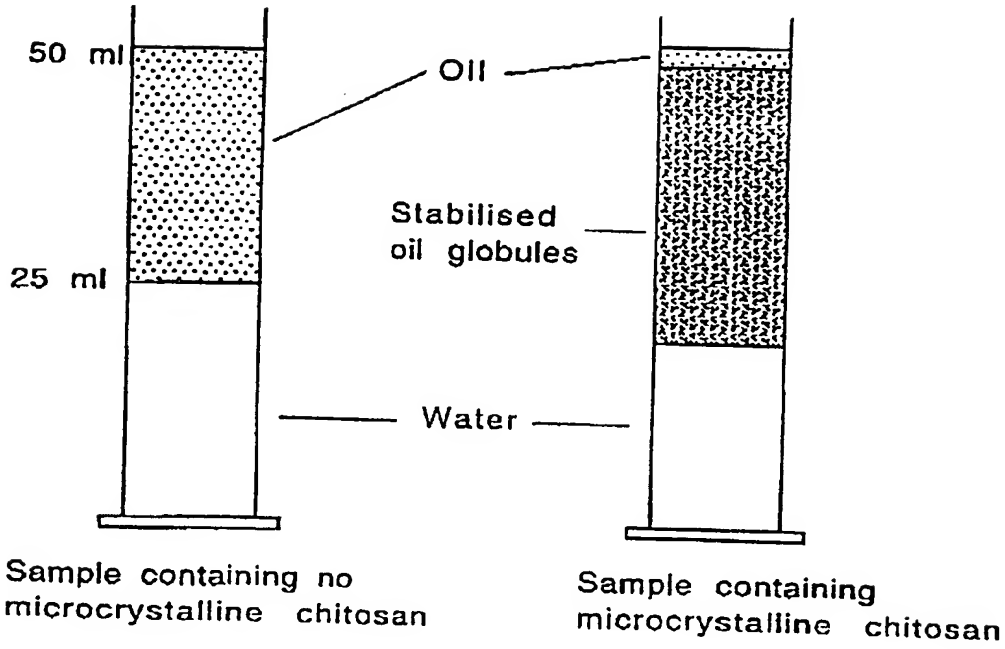
50 ml
25 ml
Oil
Stabilised
oil globules
Water
Sample containing no
microcrystalline chitosan
Sample containing
microcrystalline chitosan

Figure 1

INTERNATIONAL SEARCH REPORT

Inter ɔnal Application No
PCT/GB 99/00024

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/715 A61K33/06 A61K9/48 A61K9/28 A23L1/308

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 4 432 968 A (PAGE JUDITH L ET AL) 21 February 1984 see column 2, line 45-60 see column 3, line 20-34 see column 11, line 54-55 see claims 1,43 ---	1,4,23, 24,26,27 2-4,6-17
Y	WO 95 35100 A (DANBIOSYST UK ;WATTS PETER (GB)) 28 December 1995 cited in the application see page 3, line 25-29 see page 5, line 9-14 see page 5, line 20-25 see page 6, line 4-7 see page 6, line 24 - page 7, line 2 see claims --- -/--	2-4,6-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 April 1999	07/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	La Gaetana, R

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/GB 99/00024

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 775 450 A (AR TRADE INVEST SA) 28 May 1997	17
A	see page 2, line 1-17 see page 3, line 17-33 see claim 6	5
A	US 5 540 917 A (ISLER DOROTHEA ET AL) 30 July 1996 see column 1, line 10-30 see column 2, line 53-58 see column 2, line 63-66 see column 3, line 57 see claims	21,22,25
P,A	WO 98 34625 A (KIVEKAES OLLI ;HAEKLI HARRI (FI); MAEKINEN ELINA (FI); NOVASSO OY) 13 August 1998 see page 4, line 1-5 see page 5, line 23-26 see page 9, line 28-29 see claims 1,15,16	1-4,17, 19,23, 24,26
P,A	DATABASE WPI Section Ch, Week 9905 Derwent Publications Ltd., London, GB; Class B04, AN 99-054268 XP002101230 & JP 10 306028 A (HARAGUCHI K) , 17 November 1998 see abstract	1-4,17, 23,24,26

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/00024

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: –
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte .onal Application No
PCT/GB 99/00024

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		NZ 247927 A	26-09-1995
		ZA 9304351 A	27-12-1993
WO 9834625 A	13-08-1998	FI 970499 A	07-08-1998
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